Effect of Nitroglycerin on Exercise-induced Abnormalities of Left Ventricular Regional Function and Ejection Fraction in Coronary Artery Disease

Assessment by Radionuclide Cineangiography in Symptomatic and Asymptomatic Patients

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SUMMARY The effects of nitroglycerin (TNG) on exercise-induced abnormalities of left ventricular wall motion and ejection fraction are unknown in symptomatic and asymptomatic patients with coronary artery disease (CAD). In the present investigation radionuclide cineangiographic studies were performed in 47 patients with CAD (14 without angina during exercise) and in 25 normal subjects. All CAD patients, including those without symptoms, demonstrated regional wall motion abnormalities during exercise. In all patients, ejection fraction (EF) also responded abnormally to exercise: EF decreased from 48% at rest to 36% during exercise

Nitroglycerin can prevent angina pectoris when administered before exertion. However, the effects of the drug on wall motion and ejection fraction abnormalities induced by exercise are unknown. Moreover, we do not know the effects of nitroglycerin on regional function and ejection fraction during exercise in the absence of angina.

We have developed a noninvasive radionuclide imaging system1-4 that permits accurate assessment of regional left ventricular function and ejection fraction during exercise.5-7 Our early studies8 suggested that regional dysfunction of coronary artery disease can be induced by exercise even in the absence of symptoms. Therefore, we have now employed this technique in a large group of patients with coronary disease to determine the effects of exercise on myocardial function in patients with and without symptoms. In addition, we have studied the effects of nitroglycerin on myocardial dysfunction induced by exercise in both symptomatic and asymptomatic patients.

Methods
We performed studies in 45 men and two women, 39 to 68 years of age, admitted to the National Heart, Lung, and Blood Institute for evaluation of possible coronary artery disease (CAD). No other cardiac abnormality was present in any patient. All studies were performed at least 48 hours after cessation of propranolol, and at least four hours after nitroglycerin administration. Each patient underwent coronary arteriography and contrast left ventriculography at rest8,9 within two days after radionuclide scintigraphy. All patients admitted to the Institute between April 1976 and January 1977 were included in the present study if on contrast angiography they had ≥ 50% stenosis of at least one coronary artery and did not require continuous propranolol while in the hospital. Of the 47 patients with CAD: 1) 37 had experienced angina pectoris up until the time of admission and 33 of these patients developed angina during exercise scintigraphy; the other four patients did not develop angina during exercise scintigraphy; 2) seven had a history of angina pectoris, myocardial infarction or both, but were without symptoms for at least two months prior to admission; none of these patients developed symptoms during exercise scintigraphy; 3) three patients with angiographically demonstrated CAD had no history of angina or myocardial infarction. Each of these three had been admitted for coronary arteriography as part of other research protocols. These patients also did not develop symptoms during exercise scintigraphy. In this study, then, 14 patients did not develop symptoms when radionuclide cineangiography was performed during exercise; this group will be referred to as the asymptomatic group.

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In addition, 25 normal subjects, 35 to 63 years of age, without clinical, electrocardiographic or echocardiographic evidence of cardiovascular or other systemic disease were studied. Each normal subject had normal left ventricular systolic function at rest, as evidenced by an ejection fraction of > 60% by echocardiography.10

Gated cardiac scintigraphy was performed with subjects in the supine position at rest and during exercise as previously described.9 In this procedure, human serum albumin labeled with 10 mCi of radioactive technetium (Tc99m) is administered intravenously. After the tracer has equilibrated in the blood pool, a conventional Anger camera (field of view = 254 mm diameter), equipped with a high-sensitivity parallel hole collimator, is oriented in the modified left anterior oblique position1-2 (to isolate the left ventricle in the field of view) for imaging both at rest and during exercise. Imaging is accomplished by the use of our previously described computer-based electrocardiographically-gated procedure,1,5-11 which has been modified to reduce data processing time and the interval required to achieve statistical reliability.4-5,12 The spatial resolution of this system is one centimeter.

When this procedure is employed, data are collected and concurrently organized into a series of images (framing rate up to 100 frames/sec) residing in the core memory of the computer and spanning the average cardiac cycle. While data are being acquired, these images can be displayed in rapid sequence, that is, in endless-loop flicker-free movie format, so that qualitative information regarding spatial and temporal variations of the cardiac chambers is immediately accessible. Visually interpretable information is produced within 30 seconds of the onset of data collection, and statistically reliable results within one to two minutes.4,12 The rapidity of data collection permits the procedure to be applied to studies during exercise, even in patients with coronary artery disease in whom exercise-induced ischemia and angina might preclude prolonged exercise and imaging.5

While the cardiac images are being created, the computer simultaneously analyzes the acquired data to produce a time-activity curve with high (10 msec) temporal resolution.1-3,5,11,12 Corrections for background activity are made as previously described.1-3,11 Since blood radioactivity is proportional to blood volume, after correction for background the time-activity curve in fact represents a measure of left ventricular volume versus time. Therefore, once the physician has identified the left ventricle in the end-diastolic movie frame, quantitation of left ventricular volume change with time can be performed.

Statistically reliable information is obtained by summing the radioactivity in the ventricle during many beats. After each cardiac cycle the length of the RR interval is automatically examined to determine if it lies within a physician-selected temporal beat-length “window.” Cycles falling outside this window are rejected to prevent distortion of the time-activity curve by premature beats. The movie can be similarly windowed. Ejection fractions obtained by this method show excellent correlation with those obtained by contrast angiography with the patient at rest (r = 0.92).13

After the images and time-activity curves were obtained at rest, the subjects began to pedal a bicycle ergometer. A restraining harness was employed to prevent significant patient motion under the camera during exercise. Exercise loads employed had been found at a previous practice session to cause angina within two to six minutes. In normal subjects or in patients without angina, exercise loads were increased in stepwise fashion at two-minute intervals, culminating in loads that produced heart rates previously determined to be maximal for each subject. Subjects then exercised until limited by fatigue. Imaging was begun when the heart rate reached 5 to 10 beats per minute below the rate previously associated with angina or, in patients without angina, 10 beats per minute below maximal heart rate.

Imaging continued for at least two minutes, until development of fatigue or typical angina of severity customarily causing the patient to stop exercising. Since symptoms most often developed and exercise was stopped at heart rates considerably lower than those reached by normal subjects at peak exercise, imaging and analysis were undertaken in normal subjects at several intervals during exercise at submaximal as well as maximal heart rates. In all subjects, heart rate and blood pressure, obtained by sphygmomanometry, were recorded.

It might be anticipated that patient motion during exercise could distort images and obscure wall motion. However, this is not a practical problem when the technique is used in performing qualitative estimation of function of large regions of the left ventricle. That this is true is indicated by 1) the previously demonstrated accuracy of wall motion analysis with this technique in indicating the presence or absence of coronary artery disease in a given patient (that is, in separating normal from abnormal10-17) and 2) the very good correlation between the presence of a regional abnormality during exercise and the presence of a ≥ 50% stenosis of the coronary artery supplying this region, with no false positives having been noted.4 As noted above, patient motion is minimized with the use of a restraining harness. When this method is employed the amount of movement of two cobalt line sources placed on the subject’s chest is within the limits of spatial resolution of the method. That is, when the two line sources are placed one cm apart, they can be perceived as separate as easily during exercise as at rest; hence, perception of differences in motion is at most minimal when studies at rest and during exercise are compared.14 Moreover, with the radionuclide technique, visual perception of regional function depends not only on perception of edge motion, but also on perception of volume change (brightness of the image) in the region adjacent to the edge (the latter change being relatively great in association with relatively small changes in edge motion); therefore absence of high spatial resolution is not an important limitation with the radionuclide technique.

After the initial rest and exercise studies, patients and normal subjects were allowed to rest for 30 to 40 minutes, after which another movie was taken during rest; 0.4 mg of nitroglycerin was then administered sublingually to 28 patients and 11 normal subjects. If resting heart rate manifested a sustained increase of ≥ 5 beats/minute within 3–4 minutes, and systolic blood pressure fell or did not rise, studies were repeated with the patient at rest. If heart rate did not rise, one or two additional doses of 0.4 mg of nitroglycerin were given until a rate change was seen, and studies then commenced. After studies were performed at rest, 0.4 mg of nitroglycerin was again administered (approximately 10 minutes after the first dose) and studies were repeated during
exercise, employing the same ergometric load as had been achieved without medication. In four patients data were obtained at an additional higher exercise load, since the symptoms that led to cessation of exercise pre-nitroglycerin did not appear post-nitroglycerin. In addition, eight patients with CAD and nine normal subjects underwent two rest-exercise sequences, separated by 30 to 40 minutes, without nitroglycerin therapy.

After completion of imaging, left ventricular ejection fractions at rest and during exercise were determined by the computer from the time-activity curves. Regional left ventricular function, at rest and during exercise, was determined visually from movies by each of three blinded observers who were unaware of the results of coronary angiography, or the presence or absence of nitroglycerin therapy. All three observers consistently agreed on the presence or absence of regional dysfunction in each patient. In five of the studies in the 47 patients with CAD, one of the observers failed to note regional abnormalities. In each case, the other two identified regional abnormalities and unanimous agreement was reached by the three prior to unblinding.

Since images during exercise were constructed from images obtained in the modified left anterior oblique position, function of the anteroseptal and anterolateral ventricular walls was evaluated from the movie. Movie assessment of other surfaces of the heart can be achieved by imaging with the camera oriented in positions other than modified left anterior oblique; however, in the present study we did not utilize other camera orientations; rather, we further assessed regional function from count based “difference images” created by subtracting the end-systolic image from the end-diastolic image, as previously described. In the resulting difference image the intensity (brightness) of each region of the image is proportional to the absolute change in radioactive emissions (volume) between diastole and systole in that region. Normally the entire image appears bright except for relative darkness in the region near the outflow tract where end-systolic volume is greatest. On the left anterior oblique view this region corresponds to the upper left corner of the LV difference image. Thus, in the left anterior oblique view, a region of darkness located centrally in the difference image and surrounded by bright regions (that is, a non-edge-bordered defect) would necessarily represent either a posterobasal or an anterobasal region from which blood is not being ejected normally (i.e., is not being ejected as great a quantity as from surrounding regions). Since a region in the center of the ventricle should normally eject the largest absolute quantity of blood, a non-edge-bordered defect in the difference image is particularly predictive of regional dysfunction.

In order to assess regional abnormalities semiquantitatively for purposes of comparison, function of the anteroseptal and anterolateral regions were graded separately, each on a scale of 0 to 3, as follows: 0 = normal, 0.5 = mild hypokinesia, 1 = severe hypokinesia, 2 = akinesia, 3 = dyskinesia. Non-edge-bordered defects on the difference images were scored only as 0 (absent) or 1 (present). The score for any one region was the average of the scores of each of the three observers, rounded to the nearest half integer. The score for the entire ventricle was the sum of the scores for each of the three regions. Thus, the maximum possible score for each ventricle (i.e., the worst recordable function) would be 7 (3 for anteroseptal dysfunction, 3 for anterolateral dysfunction and 1 for an abnormal difference image).

Statistical comparisons were obtained by using Student's t-test and the Fisher exact test.

Results

Abnormalities in regional function were present at rest in 17 patients and absent in 30. During exercise, at least one new region of dysfunction appeared in all those with normal ventricles at rest; moreover, at least one new or intensified region of dysfunction appeared during exercise in all but seven of those in whom regional abnormalities were noted at rest. (In the remaining seven who were abnormal at rest, changes in regional function from rest to exercise could not be detected, though ejection fraction fell during exercise.) This was true not only in those patients who developed angina during exercise, but also in all 14 patients who did not develop angina. Six of the latter group had normal ventricles at rest. The mean regional function index for all 47 patients was 1.5 at rest and 3.0 with exercise (P < 0.001). In all cases coronary arteriography revealed stenosis of ≥ 50% in coronary arteries supplying regions noted to function abnormally on radionuclide cineangiography. No region supplied by a normal coronary artery was found to be abnormal. None of the normal subjects manifested regional abnormalities either at rest or during exercise.

Exercise also caused changes in left ventricular ejection fraction. Directional changes in ejection fraction correlated with coronary blood flow, and intensity of exercise (Fig. 1).

**FIGURE 1.** Effect of maximal exercise on left ventricular performance as determined by ejection fraction. CAD = coronary artery disease, Ex = maximal exercise, Θ = average ejection fraction.
well with the presence or absence of regional dysfunction (fig. 1). Thus, in normal subjects, none of whom had regional dysfunction, ejection fraction increased significantly from rest to exercise with a significant ($P < 0.001$) rise noted no matter which of the three levels of exercise was employed (average ejection fraction = $57 \pm 1$ (se) % at rest, $66 \pm 6\%$ at HR 90–105, $69 \pm 7\%$ at HR 105–120 and $71 \pm 2\%$ at maximal exercise). In contrast, ejection fraction fell from rest to exercise in 42 of the 47 patients ($P < 0.001$). (All 47 had regional abnormalities.) For the entire group, ejection fraction at rest was 48% and fell to 36% with exercise ($P < 0.001$ as compared with rest and with the change from rest to exercise in normal subjects). In four of the 47 patients, ejection fraction rose slightly during exercise, but each of these four patients had an easily recognized region of dysfunction that appeared with exercise. In one patient ejection fraction did not change from rest to exercise. Only two of the patients with CAD developed ejection fractions during exercise that were in the range attained by the normal subjects. Again, however, both developed a regional wall abnormality during exercise. (Normal subjects developed ejection fractions of 58% to 93% during exercise; no ejection fraction below 58% was recorded in this group at any of the three levels of exercise at which assessments were made.)

Each of the 14 patients who did not develop angina during exercise testing demonstrated regional dysfunction; 13 experienced a reduction in left ventricular ejection fraction with exercise. The one asymptomatic patient in whom ejection fraction rose (to 34%) had a 32% ejection fraction at rest with marked wall motion abnormalities at rest and during exercise.

When nitroglycerin was administered, regional function at rest improved in patients with CAD, as noted previously by others. For those with regional dysfunction at rest, the regional function index at rest before nitroglycerin was 3.0 and was 2.5 after nitroglycerin ($P < 0.001$). In addition, with exercise a marked improvement in regional left ventricular function was noted after nitroglycerin as compared with exercise before nitroglycerin. For all 47 patients regional function index was 3.0 during exercise before nitroglycerin and 1.5 during exercise after nitroglycerin ($P < 0.001$; figs. 2 and 3a). In normal subjects no abnormalities in regional function were noted after nitroglycerin.

Improvement in ejection fraction accompanied the reduction in regional dysfunction in patients with CAD. At rest, left ventricular ejection fraction rose from an average of 45% before nitroglycerin to an average of 50% ($P < 0.02$) after nitroglycerin. During exercise (figs. 3b and 4) the improvement was more striking: average ejection fraction during exercise after nitroglycerin was 48%, significantly higher than during exercise before nitroglycerin (average ejection fraction 36%, $P < 0.001$ as compared with exercise after nitroglycerin). In normal subjects, at rest, ejection fraction invariably rose after nitroglycerin (average 57% without nitroglycerin and 68% with nitroglycerin, $P < 0.001$). However, during exercise ejection fraction was unaltered by nitroglycerin. This result is significantly different from that found in the group of patients with CAD ($P < 0.001$, fig. 4).

Among the eight patients with CAD in whom rest and exercise studies were repeated without nitroglycerin neither the regional function index nor the ejection fraction during the second exercise was significantly different from the values obtained during the first exercise (fig. 5). Similarly, ejection fraction did not change significantly in the nine normal subjects in whom exercise was repeated without nitroglycerin (fig. 5).

As per the protocol requirements, heart rate invariably increased at rest with nitroglycerin in patients and normal subjects. In patients with CAD, heart rate at maximum exercise was slightly but significantly higher after nitroglycerin, as compared with exercise prior to nitroglycerin (112 beats/minute versus 116, $P < 0.02$). Systolic arterial blood pressure response during exercise was modestly but significantly reduced after nitroglycerin (158 mm Hg vs 147 mm Hg, $P < 0.01$).

Discussion

Several conclusions can be drawn from our results. First, the data indicate that radionuclide cineangiography is a sensitive method for determining the presence of functionally important stenoses of the coronary arteries. Abnormalities in regional function were noted during exercise in all 47 patients who had narrowing of $\geq 50\%$ of at least one major
coronary artery. No abnormalities in regional function were noted in normal subjects. Moreover, the patients with coronary artery disease consistently manifested a reduction in response of left ventricular ejection fraction to exercise. Thus, in contrast to the response of normal subjects, ejection fraction fell from rest to exercise in 42 of 47 patients, and ejection fraction during exercise was below the normal range in 45 (fig. 1).

Our results also indicate that radionuclide cineangiography can detect abnormalities of regional function and of ejection fraction during exercise even in the absence of symptoms. Thus, such abnormalities were present in each of the 14 patients who did not develop angina during exercise. Three of these patients had no history of cardiac symptoms prior to hospital admission. These findings confirm previously reported indications that exertion-induced myocardial ischemia may occur even if the patient does not perceive chest pain. Previous studies have demonstrated that

FIGURE 3. a) Unretouched selected frames, in sequence, from a radionuclide cineangiogram taken in a patient with three vessel coronary artery disease who did not develop angina pectoris during exercise. Upper sequence is taken from movie obtained with the patient at rest and demonstrates normal LV function; middle sequence is taken from a movie obtained during exercise without nitroglycerin, which demonstrated anteroseptal and anterolateral wall motion abnormalities; these were much improved in the lower sequence, obtained during exercise with nitroglycerin. ED = end-diastolic frame, ES = end-systolic frame, DIFF = difference image (created by electronic subtraction of end-diastolic counts from end-diastolic counts, with intensity (brightness) proportional to the change in volume between end diastole and end systole in each region of the heart). Difference images are normal during rest and during exercise with nitroglycerin, but a central non-edge-bordered defect is present during exercise without nitroglycerin. Ao = aorta, PA = pulmonary artery, RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle. b) Time-activity curves from studies depicted in (a). EDV denotes end-diastolic volume. Note that ejection fraction (EDV-end systolic volume)/EDV decreases during exercise without nitroglycerin, an effect which is largely ameliorated by administration of nitroglycerin before exercise.
electrocardiographic ST-segment abnormalities can appear during exercise in asymptomatic individuals who have underlying severe coronary artery disease. In addition, left ventricular end-diastolic pressure has been shown to increase during exercise or atrial pacing in patients with coronary artery disease, even at levels of stress that do not produce angina. The results of the present investigation, therefore, extend these earlier observations by providing evidence compatible with the concept that ischemia sufficient to affect both regional and global left ventricular mechanical function can occur in the absence of ischemic symptoms.

We have found, as have other investigators, that in patients with CAD nitroglycerin administration can improve regional left ventricular function and ejection fraction while the patient is at rest. Nitroglycerin can also prevent angina pectoris when administered prior to exertion, presumably by improving the balance between myocardial oxygen supply and demand. Therefore, the drug would be expected to relieve ischemia-induced left ventricular dysfunction. However, although nitroglycerin reduces exercise-induced electrocardiographic abnormalities and improves left ventricular hemodynamics during exercise and atrial pacing in such patients, its effects on regional function and on ejection fraction during exercise have not been studied previously. Thus, the third important observation derived from this study is that in patients with CAD, the exercise-induced abnormalities in ejection fraction and regional left ventricular wall motion are improved, and at times normalized, by nitroglycerin administration (figs. 2-4).

The mechanisms responsible for the beneficial effects of nitroglycerin cannot be elucidated by the findings of the present investigation. However, it is of interest that while nitroglycerin increased ejection fraction in normal subjects at rest, the drug did not change ejection fraction during exercise. If nitroglycerin improves systolic function solely by lowering impedance to left ventricular ejection it might have been anticipated that normal individuals would have behaved, at least to some extent, like the patients with coronary artery disease. Since they did not, it is possible that an additional mechanism, other than the physical effect of reduction in impedance to left ventricular ejection, may be operative. First, reduction in preload and afterload by nitroglycerin would be expected to reduce myocardial oxygen demand, thereby reducing ischemia and permitting improvement in ventricular function. In addition, it is possible that nitroglycerin might reduce ischemia by improving myocardial oxygen supply, perhaps by increasing coronary collateral flow in a manner analogous to that demonstrated during experimental acute coronary artery occlusion. However, we cannot rule out the possibility that the complex mechanical effects of nitroglycerin, derived from the alterations it produces on preload and afterload, are solely responsible for the beneficial actions of the drug we observed.

In summary, our findings indicate that in patients with coronary artery disease, abnormalities in regional left ventricular function and in ejection fraction develop during exercise, even at levels of exertion that do not cause angina. Moreover, these abnormalities can be detected with high sensitivity by radionuclide cineangiography. Finally, exercise-induced ischemic dysfunction can be significantly mitigated by prophylactic therapy with nitroglycerin, even during exertion which is not accompanied by pain.

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References

The Prognostic Implications of Acute Myocardial Infarct Scintigraphy with $^{99m}$Tc-Pyrophosphate

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SUMMARY The predictive value of myocardial scintigraphy with $^{99m}$Tc-pyrophosphate was studied in 100 patients admitted to the coronary care unit with suspected acute myocardial infarction. None of the 21 patients with normal scintigrams had acute myocardial infarction by other criteria. Fifty-five percent of patients with diffuse uptake (pattern B), 73% of patients with focal uptake (pattern C) and all patients with intense focal uptake (pattern D) and massive uptake (pattern E) had acute infarction. The complication rate in the hospital and after discharge (mean followup: 6.1 months) for patients with pattern E was 88% compared to 42% for D, 30% for C, 36% for B and 10% for patients with normal scintigrams (A). For patients with acute infarction with patterns C, D and E, the complication rate rose with increasing size of the myocardial uptake of $^{99m}$Tc-pyrophosphate. In addition to its diagnostic potential, scintigraphy provides prognostic information which is useful for patient triage and for therapeutic decisions early in the evolution of the infarct.

PUMP FAILURE, the primary cause of in-hospital death in patients with acute myocardial infarction, reflects the extent of cellular necrosis. Recently, a scintigraphic technique has been developed using radiopharmaceuticals which sequester in acutely damaged myocardium. Since the extent of uptake of the radiotracer has correlated well with the size of infarction, recent acute infarct scintigraphy might be expected to have predictive value in assessing patients with acute myocardial infarction. In this study, we have correlated the diagnosis and complication rate of patients admitted to the coronary care unit with suspected acute infarction with the results of scintigraphy performed using $^{99m}$Tc-pyrophosphate.

Methods One hundred patients admitted to the coronary care unit with the possible diagnosis of acute myocardial infarction were studied after informed consent had been obtained.


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